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PTO/SB/21 (6-99)

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(to be used for all correspondence after initial filing)

Application Number	09/989,725
Filing Date	NOVEMBER 20, 2001
First Named Inventor	AVI J. ASHKENAZI
Group/Art Unit	1647
Examiner Name	HAMUD, FOZIA M.
Total Number of Pages in This Submission	
Attorney Docket Number	39780-2730 P1C71

ENCLOSURES ***(check all that apply)***

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Version With Markings Showing Changes
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
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- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] **APPEAL COMMUNICATION TO GROUP** ***(APPEAL NOTICE, BRIEF, REPLY BRIEF)***
- [ ] Proprietary Information
- [ ] Status Letter
- [x] **ADDITIONAL ENCLOSURE(S)** ***(PLEASE IDENTIFY BELOW):***
- [x] **EVIDENCE APPENDIX ITEMS 1-5: ARTICLES BY: KAHAN, ET AL.; PICOTTI, ET AL.; CAMPO, ET AL. & NISHIOKA, ET AL.; DECLARATION OF SHERMAN FONG WITH EXHIBITS A-E; and RETURN POSTCARD**

Remarks

AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT 08-1641 FOR ANY FEES DUE IN CONNECTION WITH THIS PAPER, REFERENCING ATTORNEY'S DOCKET NO. 39780-2730 P1C71.

SIGNATURE OF APPLICANT, ATTORNEY OR AGENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	) Examiner: Hamud, Fozia
Avi ASHKENAZI, *et al.*	) Art Unit: 1647
Application Serial No. 09/989,725	) Confirmation No: 2364
Filed: November 20, 2001	) Attorney's Docket No. 39780-2730 P1C71
For: **NUCLEIC ACIDS ENCODING PRO1375 POLYPEPTIDES**	) **Customer No. 35489**

EXPRESS MAIL LABEL NO.: EV 582 624 825 US
DATE MAILED: MAY 30, 2006

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' BRIEF

MS: APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 15, 2004, the Examiner made a final rejection to pending Claims 119-127, 129-132 and 134-138. A Notice of Appeal was filed on May 5, 2005 and Appeal brief was filed on October 3, 2005.

A Notification of Non-Compliant Appeal Brief was mailed May 1, 2006, which stated that the amendment to the claims filed after the Final Office Action did not fit with the criteria of MPEP 1206. The following amended appeal brief has been corrected to include the claim set as entered by the Examiner before the Final Office Action.

The following constitutes the amended version of Appellants Brief on Appeal.

1. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the patent application U.S. Serial No. 09/941,992 recorded November 16, 2001, at Reel 012176 and Frame 0450.

2. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO1375". There exists one related patent application, U.S. Serial No. 09/997,573, filed November 15, 2001 (containing claims directed to PRO1375 polypeptides). This application is also under final rejection from the same Examiner and based upon the same outstanding rejections, an appeal of these final rejections is being pursued independently and concurrently herewith.

3. STATUS OF CLAIMS

Claims 119-127, 129-132 and 134-138 are in this application.

Claims 1-118, 128 and 133 are canceled.

Claims 119-127, 129-132 and 134-138 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims involved in the present Appeal is provided as Appendix A.

4. STATUS OF AMENDMENTS

The claims involved in the appeal have been amended by an amendment filed concurrently with this appeal brief wherein Claims 120 - 124 have been amended to label the subparts of the claims from (a) through (f) correctly and the functional recitations of Claims 119-123 have been amended for clarity. The claims listed in the Appendix incorporate this amendment.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to a nucleic acid that encodes a polypeptide of SEQ ID NO:418 referred to in the present application as "PRO1375"; a nucleic

acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide; a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO:418; the nucleic acid sequence of SEQ ID NO:417, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:417; or the full-length coding sequence of the cDNA deposited under ATCC accession number 203115 (Claims 124-127 and 129). The PRO1375 polypeptide was shown in the present application to induces proliferation of stimulated T-lymphocytes in a mixed lymphocyte reaction as compared to controls which is set forth in the specification in Example 151. The invention is further directed to polypeptides having at least 80%, 85%, 90%, 95%, or 99% nucleic acid sequence identity to: a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418; a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide; a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO:418; the nucleic acid sequence of SEQ ID NO:417, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:417; or the full-length coding sequence of the cDNA deposited under ATCC accession number 203115, wherein the polypeptide encoded by said nucleic acid induces proliferation of stimulated T-lymphocytes in a mixed lymphocyte reaction (Claims 119-123).

The cDNA nucleic acid and isolation of clones encoding PRO1375 is described in the specification at, for example, Example 135, page 511 of the specification, in Figure 299 and SEQ ID NO: 417. Hybridization conditions for nucleic acids hybridizing to SEQ ID NO: 417 are discussed on page 275, line 5, page 312, line 23 to page 313, line 4 and Example 139 (Claims 132, 134). The full-length PRO1375 polypeptide is described in the specification at, for example, page 40, line 9-13, page 275, line 1 to page 277, line 3; in Figure 300 and in SEQ ID NO:418. Page 302, lines 28-31 of the specification provides the description for Figures 300 and 299. That PRO1375 is a polypeptide having homology to PUT2, putative protein 2 is described at page 40, line 9-13.

PRO nucleic acid variants having at least about 80% sequence identity to a DNA molecule that encodes the same mature polypeptide encoded by any of the disclosed human cDNAs deposited with the ATCC are described in the specification at, for example, page 284, line 30, to page 285, line 5 and page 308, line 7 to p 311, line 10. Methods for selecting a vector are generally set forth in the specification at, for example, in Examples 140-143 and page 376,

line 12 onwards (Claims 137-138), and describes the expression of PRO nucleic acids in various host cells, including *E. coli*, yeast and Baculovirus-infected insect cells. Methods for selecting a vector are generally set forth in the specification at, for example, page 378, line 8, to page 380, line 11 (Claims 135 and 136).

Example 151 shows that PRO1375 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO1375 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore would have utility in the treatment of conditions where the enhancement of an immune response would be beneficial. In addition, Example 165 shows the ability of PRO1375 to stimulate an immune response and induce inflammation at the site of injection in the skin vascular permeability assay, using the hairless guinea pig injected with the Evans blue dye as a model system.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether Claims 119-127, 129-132 and 134-138 should be accorded the priority of U.S. provisional application Serial No. 60/144758, filed July 20, 1999.

II. Whether the data generated in the MLR assay (Example 151) satisfies the utility requirement set forth in 35 U.S.C. § 101 and the "how to use" prong of the enablement requirement set forth in 35 U.S.C. § 112, first paragraph for the invention claimed in Claims 119-127, 129-132 and 134-138.

III. (i) Whether Claims 119-127, 129-132 and 134-138 are patentable under 35 U.S.C. §102(b) over WO00/18904, (published June/2000); WO99/63088, (published September/1999); WO00/00610, (published June/2000); WO00/00506, (published June/2000).

(ii) Whether Claims 119-125, 127, 129-138 are patentable under 35 U.S.C. §102(a) over EP1130094, (published September/2001).

7. ARGUMENT

Summary of the Arguments:

Issue I: Priority

The instant application has not been granted the earlier priority date on the grounds that "the MLR assay fails to provide a specific and substantial utility or well established utility for the claimed invention to satisfy the requirements under 35 U.S.C.§ 101/112, first paragraph, because it does not teach how one of ordinary skill in the art could use the claimed invention." (Page 3 of the Final Office Action mailed November 24, 2004).

Appellants submit that data derived from the mixed leukocyte reaction (MLR) assay was first disclosed in U. S. Application Serial No. 60/144,758 filed July 20, 1999 for the claimed PRO1375 polypeptides. Appellants further submit that, the disclosure of U. S. Application Serial No. 60/144,758 is sufficient to establish patentable utility for the claimed polypeptides for the same reasons discussed below under the section on Issue II: Utility/ Enablement. The currently pending claims are therefore entitled to the July 20, 1999, priority date of U.S. Provisional Application No. 60/144,758 in which the results of the MLR assay were first disclosed.

Issue II: Utility/ Enablement

Appellants submit that patentable utility for the nucleic acids encoding the PRO1375 polypeptide is based upon the data derived from the mixed leukocyte reaction (MLR) assay. Example 151 shows that PRO1375 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO1375 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore has utility in the treatment of conditions where the enhancement of an immune response would be beneficial. At the priority date of the present application it was well known that stimulators of T-cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection, as well as in the treatment of cancers such as melanoma.

Appellants have also submitted with their Response filed August 5, 2004, the Declaration by Dr. Sherman Fong, a unquestionable expert in the field, which provides examples of important clinical applications for immune stimulants which have shown activity in a mixed lymphocyte reaction assay, such as the chemokine IL-12, which finds utility in the treatment of

melanoma due to its ability to stimulate immune response. Dr. Fong states that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Despite Dr. Fong's unequivocal statement and the teachings of the present application, the Examiner has asserted that "the MLR is an *in vitro* model for allogenic reaction, this assay has not been correlated with a specific disease or disorder.... MLR is typically used for determining histocompatibility in a individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders." In support of this assertion, the Examiner has cited references by Kahan *et al.*, Picotti *et al.* and Campo *et al.* The Examiner also takes issue with Dr. Fong's declaration and quotes Picotti *et al.* and Nishioka *et al.* to show that "the fact that an agent stimulates or inhibits T-cells in the MLR assay, is not sufficient to explain the role of said agent in the immune system." (Page 12, Final Office Action mailed November 15, 2004).

First of all, the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

The Examiner has not shown that a lack of correlation typically exists between the results of the MLR assay *in vitro* and immunomodulatory activity *in vivo* by quoting the references Kahan *et al.*, Picotti *et al.*, Campo *et al.* and Nishioka *et al.* In fact, Appellants submit that the teachings within Picotti *et al.*, Campo *et al.* and Nishioka *et al.* support the Appellants' position that the *in vitro* MLR assay **can** and **has been** successfully used to identify compounds having immunomodulatory activity *in vivo.* Therefore, based on such teachings, one of ordinary skill in the art would find it 'more likely than not' that those molecules which test positive in the disclosed MLR assay would have real-world therapeutic utility as immunostimulants *in vivo;* that is, how to use the claimed polypeptides for the treatment of viral infections and cancer, without any undue experimentation. Thus the Patent Office has failed to meet its initial burden of proof

that Appellants' claims of utility are not substantial or credible.

Appellants add that the Examiner has misinterpreted the focus of the assay disclosed in the specification. The purpose of the assay is not to test the properties of the stimulator cells, as in a typical MLR assay, but to test the ability of a protein, such as PRO1375, to enhance the expected response of the T cells, thus demonstrating general immunostimulant activity.

Regarding the enablement rejection, Appellants note that the claimed variants, in addition to having at least 80% nucleic acid sequence identity to SEQ ID NO:417, also have the functional recitation that "said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction." Thus the claimed variants all share the disclosed utility of the PRO1375 polypeptide as an immunostimulant. The specification provides ample guidance to allow the skilled artisan to identify those nucleic acids encoding the polypeptide variants which meet the recitations of the claims, including a detailed protocol for the MLR assay. Accordingly, one of ordinary skill in the art would understand how to use the recited the nucleic acids encoding the polypeptide variants without any undue experimentation.

Accordingly, Appellants submit that the MLR assay suffices to provide patentable utility for the subject matter of the instant claims and that, in view of this, one of skill in the art would know exactly how to use the polypeptides encoded for by the claimed nucleic acids, for instance, in the treatment of viral infections or cancer, without any undue experimentation.

Issue III: Anticipation by WO00/18904, WO99/63088, WO00/00610, WO00/00506 and further, anticipation by EP1130094

(i) Claims 119-127, 129-132 and 134-138 stand rejected under 35 U.S.C. §102(a) as being anticipated by WO00/18904, (published June/2000); WO99/63088, (published September/1999); WO00/00610, (published June/2000); WO00/00506, (published June/2000).

(ii) Claims 119-127, 129-132 and 134-138 stand further rejected under 35 U.S.C. §102(a) as being anticipated by EP1130094, (published September/2001).

The instant application claims priority to U.S. Provisional Application Serial No. 60/144,758, filed on July 20, 1999, over six months before the publication date of WO00/18904, WO00/00610, WO00/00506, and at least one month before the publication date of WO99/63088. U.S. Provisional Application Serial No. 60/144,758 first disclosed that the PRO1375

polypeptide tested positive in the MLR assay. Further, since the instant application is entitled to priority to U.S. Provisional Application Serial No. 60/144,758, and to the effective filing date of July 20, 1999, EP1130094 is not prior art.

These arguments are all discussed in further detail below under the appropriate headings.

Detailed Arguments:

ISSUE I: U.S. Provisional Application No. 60/144,758 Satisfies the Utility Requirement of 35 U.S.C. § 101/ § 112, First Paragraph based on the results of the MLR assay

Appellants have asserted that U.S. Provisional Application No. 60/144,758, filed July 20, 1999, discloses stimulatory activity in the mixed leukocyte reaction (MLR) assay, and that the data generated in the MLR assay (shown in Example 151 of the instant specification) establishes patentable utility for the claimed nucleic acids encoding PRO1375 polypeptides. The Examiner has asserted that "(i)t is not disputed that US Provisional application 60/144,758 filed 20 July 1999 discloses the MLR assay. However, the MLR assay fails to provide a specific and substantial utility or well established utility for the claimed invention to satisfy the requirements under 35 U.S.C.§ 101/112, first paragraph, because it does not teach how one of ordinary skill in the art could use the claimed invention." (Page 3 of the Final Office Action mailed November 15, 2004).

Appellants strongly disagree and submit that, for the same detailed reasons set forth below under Issue II for Utility/ Enablement (whose arguments are incorporated by reference herein), the results of the MLR assay for PRO1375 in the specification of the provisional U.S. Application No. 60/144,758, provides at least one credible, substantial and specific asserted utility for the claimed PRO1375 polypeptides under 35 U.S.C. §101/§112, first paragraph. Accordingly, Appellants submit that the subject matter of the instant claims should be entitled to an effective priority date of **July 20, 1999**, the filing date of U.S. Provisional Application No. 60/144,758.

ISSUE II: The Data Generated in the MLR Assay Satisfies the Utility Requirement of 35 U.S.C. § 101/ § 112, First Paragraph for Claims 119-127 and 129-131

Appellants submit that the results of the MLR assay in the instant specification (and in the priority provisional application No. 60/144,758) provides at least one credible, substantial and specific asserted utility for the claimed nucleic acids encoding PRO1375 polypeptides under 35 U.S.C. §101/§112, first paragraph.

A. The Legal Standard for Utility

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

Furthermore, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

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[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners:

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[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

"If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

B. Proper Application of the Legal Standard

Appellants submit that the mixed lymphocyte reaction (MLR) assay described in Example 151 is sufficient to establish patentable utility under 35 U.S.C. §101 for the PRO1375 polypeptide and nucleic acids encoding it. The positive result for PRO1375 in the MLR assay, described in Example 151, at page 525 of the specification, demonstrates that PRO1375 is active as a stimulator of the proliferation of stimulated T-lymphocytes.

The MLR is a well-established assay for evaluating test compounds, such as the PRO1375 polypeptide, for their ability to stimulate T-lymphocyte proliferation *in vitro*, and consequently, for assessing the immune response of an individual. The MLR assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc., which is referenced in Example 74, and the entire content of which is expressly incorporated by reference into the disclosure of the present application (see page 525). In brief, in this method, an immune response results upon mixing T-cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored quantitatively by, for example, following the incorporation of tritiated thymidine during DNA synthesis, or by observing blast formation, or by other methods well known in the art.

According to the specification, positive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein. PRO1375 (SEQ ID NO: 418) tested positive in this assay, using the described criteria. Example 151 further explains that compounds which stimulate proliferation of lymphocytes in this assay "are useful therapeutically where enhancement of an immune response is beneficial." Accordingly, PRO1375 has utility in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable. Accordingly, one skilled in the art would know how to use the

polypeptides encoded for by the claimed nucleic acids, for instance, in the treatment of viral infections or cancer, without any undue experimentation.

In support of utility based upon the MLR assay, Appellants have submitted (with their Response filed August 5, 2004) the Declaration of Sherman Fong, Ph.D. Dr. Fong is an inventor of the above-identified patent application, and an experienced scientist familiar with the MLR assay, which was used by him and others under his supervision, to test the immune stimulatory or immune inhibitory activity of novel polypeptides discovered in Genentech's Secreted Protein Discovery Initiative project, including PRO1375.

The Fong Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Dr. Fong proceeds to explain (paragraph 7 of the Declaration) that dendritic cells are potent antigen-presenting cells that are able to "prime native T cells *in vivo*." Once activated by dendritic cells, the T-cells are capable of interacting with other antigen-presenting cells (B cells and macrophages) to produce additional immune responses from these cells.

As Dr. Fong states, the MLR assay of the present application

> is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously. (Paragraph 8 of the Fong Declaration.)

As Dr. Fong emphasizes, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Supportive evidence also comes from teachings in the art such as Steinman *et al.* (submitted as Exhibit B with the Preliminary Amendment filed July 12, 2004) who state that "...**medicine needs therapies that enhance immunity or resistance to infections and tumors**" (page 1, column 1, line 7; emphasis added).

In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. As Dr. Fong explains,

"IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. IL-12 was first identified in just such an MLR [Gubler et al. PNAS 88, 4143 (1991) (Exhibit C)]. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson et al. Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)] They extracted circulating white blood cells carrying one or more markers of melanoma cells, isolated the antigen, and returned them to the patients. Normally patients would not have an immune response to his or her own human antigens. The patients were then treated with different doses of IL-12, an immune stimulant capable of inducing the proliferation of T cells that have been co-stimulated by dendritic cells. Due to the immune stimulatory effect of IL-12, the treatment provided superior results in comparison to earlier work, where patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs), treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response. [Thurner et al. J. Exp. Med. 190 (11), 1669-78 (1999) (Exhibit E)]."

Dr. Fong concludes that (paragraph 10):

It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the PRO1375 polypeptides for instance, in the treatment of viral infections or cancer, without any undue experimentation, and thus, utility for the claimed nucleic acids that encode such polypeptides that are claimed in the present application, for the asserted purpose.

C. A *prima facie* case of lack of utility has not been established

As a preliminary matter, Appellants submit that, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. With respect to asserted therapeutic utilities based upon *in vitro* data, an applicant "does not have to prove that a correlation exists between a particular activity and an

asserted therapeutic use of a compound as a matter of statistical certainty" (M.P.E.P. 2107.03.). The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

(i) An in vitro assay like the MLR assay is useful for identifying compounds with immunomodulatory activity in vivo

The Examiner alleges that the fact situation in Cross *et al.* v. Iizuka *et al.* is different from the fact pattern of the instant case because Cross *et al.* v. Iizuka *et al.* discloses imidazole derivative compounds which inhibit synthesis of thromoxane synthetase, an enzyme involved in platelet aggregation. The Examiner adds that platelet aggregation is associated with several deleterious conditions in mammals such as platelet thrombosis, pulmonary vasconstriction, etc. The Examiner alleges that, on the other hand, the instant case "(t)he MLR is an *in vitro* model for allogenic reaction, this assay has not been correlated with a specific diseases or disorder." (Page 5 of the Final Office Action mailed November 15, 2004). Regarding the Appellants previous assertion that "PRO1375 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore would have utility in the treatment of conditions where the enhancement of an immune response would be beneficial," the Examiner alleges that "(the) instant specification has not established a correlation between the claimed nucleic acid or the encoded protein and any of the above mentioned disorders. The specification has not shown that the protein of the instant invention has been used to treat any of these diseases." Appellants strongly disagree.

First of all, Appellants submit that the fact situation in Cross *et al.* v. Iizuka *et al.* is entirely applicable to the instant case since, and as will be apparent in the discussions below, Appellants assert utility for PRO1375 as an immunostimulant that is useful in treating several disease conditions where the enhancement of an immune response would be beneficial, including but not limited to, viral infections, including retroviral infections like HIV or Epstein-Barr infections, as well as in the treatment of cancers such as melanoma. Appellants submit that the teachings of the specification should be evaluated through the eyes of one skilled in the pertinent art at the effective filing date of the present application. For instance, in 1998, well before the

effective filing date of July 20, 1999 of the instant application, it was well known in the art as it is today that, T-cells were highly important in the body's natural defense mechanisms for fighting infections. For example, viral infections, such as HIV infection, were well known to result in a reduced T cell count. Indeed, the count of T-cell lymphocytes was a generally accepted measure for the extent and seriousness of an HIV infection and resultant AIDS. Accordingly, stimulators of T-cell proliferation were "reasonably correlated" to the art- accepted, pharmacological utility of fighting viral infections, including retroviral infections such as HIV infections or Epstein-Barr infections.

It was also well known at the time of filing that T cells could recognize tumor antigens and kill tumors. See, for example. Thurner *et al.*, J. Exp. Med. 190:1669-1678 (1999) (submitted as Exhibit E with the Fong declaration filed August 5, 2004), which describes experimental procedures designed to treat melanoma by boosting the immune response. Accordingly, immunostimulant molecules such as PRO1375 would have an art-accepted utility in the treatment of cancers such as melanoma.

Appellants further submit that the legal standard accepts *in vitro* results as a demonstration of utility, as long as the data is "reasonably correlated" to the pharmacological utility described (for details, see Legal Standard above). For instance, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the data derived from the MLR assay is "reasonably correlated" to at least one asserted pharmacological utility in diseases such as, in the treatment of HIV or Epstein Barr infections or in the destruction of tumors in various cancers, and meets the utility standards. The art recognizes that the MLR assay is an *in vitro* assay useful for identifying compounds with immunomodulatory activity *in vivo*.

(ii) The art in fact supports the Appellants' position that an MLR result is useful for identifying compounds with immunomodulatory activity in vivo

The Examiner asserts on Page 5 that "the state of the art is such that no *in-vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficiency". In support of these assertions, the Examiner has cited references by Kahan *et al.*, Picotti *et al.* and Campo *et al.*

Appellants respectfully disagree. All three references, Kahan *et al.*, Picotti *et al.* and Campo *et al.*, study allograft rejections and immunosuppression of graft rejection using test compounds studied *in vitro*. Appellants submit that the Examiner has not correctly characterized the teachings of Kahan *et al.*, Picotti *et al.* and Campo *et al.* These references, in combination with those cited by Appellants, in fact demonstrate that the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is in fact a widely used *in vitro* assay for identifying immunomodulatory compounds.

For instance, the Examiner cited Picotti *et al.* as demonstrating that "IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result *in vitro* does not result in a measurable response *in vivo* (i.e. failure to accelerate graft rejection) see p 1459."

Appellants note that the asserted utility of PRO1375 is not to accelerate allograft rejection, which is hardly a process that medical practitioners would wish to accelerate. Thus the fact that IL-12 does not accelerate allograft rejection *in vivo* is not relevant to the utility of PRO1375. More importantly, Appellants draw the Board's attention to the fact that the failure of IL-12 to accelerate allograft rejection *in vivo* is not necessarily an indication that IL-12 does not possess general immunostimulant properties *in vivo*. For example, Picotti *et al.* confirm that "IL-12 is also a key cytokine involved in promoting cell mediated immune responses in vivo" (page 1459, col. 1). Thus, the fact that a molecule such as IL-12, which is a known immunostimulant *in vivo,* does not accelerate graft rejection supports Appellants' argument that graft rejection is a specific pathway that does not necessarily reflect general immunoregulatory function. Picotti *et al.* too draw a similar conclusion, suggesting that "the magnitude of Th1-driven alloimmune response may not correlate directly to the severity of graft rejection," perhaps because Th2-driven immune responses are more relevant to graft rejection (page 1459, col. 2). Therefore, Picotti *et*

al., provides evidence that a molecule which does not show in vivo activity in a specific graft versus host interactive pathway may still have general immunomodulatory activity.

The Examiner has further asserted that Campo *et al.* "demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*." (Page 6 of the Final Office Action mailed November 15, 2004).

Appellants respectfully point out that the Examiner has misinterpreted this statement, due to the fact that the authors refer to two different types of immunosuppressive effects. Campo *et al.* set out to look for an inhibitor of MHC *in vitro* which would have the fewest side effects *in vivo* (see Abstract). The authors note that high concentrations of zinc "impair **all** T cell and monocyte function" (page 20; emphasis added). The authors took this impairment as an indicator of toxicity, and therefore intentionally used concentrations of zinc below that at which all T-cell function was impaired, in order to identify a concentration range that would not result in toxic effects. However, that does not mean that Campo *et al.* found zinc to have no immuno-suppressive activity *in vivo*. In fact, the authors conclude, based upon their MLC results, that "zinc **could become an immunosuppressant in transplantation medicine** without toxic side effects" (page 21; emphasis added). Thus Campo *et al.* supports Appellants' position that those of skill in the art would interpret the results of MLC assays as having physiological relevance.

In fact, Appellants note that the Examiner has failed to point out several instances within these cited references wherein the authors stated that the MLR is an important method with a good predictive value. For example, Campo *et al.* teach that "the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-γ, **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection ***in vivo***.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN-γ **both *in vitro* and *in vivo***" (see page 18; emphasis added). Further, Picotti *et al.* showed that the IL-12Rβ1 subunit was critical for IL-12 driven enhanced alloimmune response ***in vitro* and *in vivo*** (see abstract). Thus, while there are instances of unpredictability using the MLR assay, there are many studies showing predictable results, including studies from Picotti, Landolfo and the IFN-γ study.

Finally, Campo *et al.* teaches that "cyclosporin A, FK506, and other substances are used to prevent graft rejection. **In vitro experiments revealed an inhibition of the MLC**" (page 16). Thus the teachings of Campo *et al.* confirm that inhibition of the MLR is observed for known immunoinhibitory molecules, that are in actual clinical use.

Thus, in fact, references Picotti *et al.* and Campo *et al.* support the Appellants' position that it is more likely than not that the *in vitro* MLR assay can be successfully used to identify compounds having immunomodulatory activity *in vivo*.

(iii) The specification provides sufficient detail to enable one of ordinary skill in the art to conclude that the instant MLR assay is useful to identify compounds having immuno-modulatory activity in vivo

The Examiner has further asserted on Page 7, line 4 of the Final Office Action that "(t)he specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion."

Appellants respectfully submit that the specification clearly discloses that PRO1375 tested positive in the MLR assay. Further, the teachings of the specification should be evaluated through the eyes of one skilled in the pertinent art at the effective filing date of the present application. For instance, in 1998, well before the effective filing date of July 20, 1999 of the instant application, it was well known in the art as it is today that, T-cells were highly important in the body's natural defense mechanisms for fighting infections. For example, viral infections, such as HIV infection, were well known to result in a reduced T cell count. It was also well known at the time of filing that T cells could recognize tumor antigens and kill tumors. The Fong Declaration reinforces the teachings of the specification that a PRO polypeptide with an activity in the MLR assay of at least 180% of the control is expected to have the type of activity exhibited by IL-12, and would therefore find practical utility as an immune stimulant. Therefore, one of ordinary skill in the art would understand that any molecule showing immunostimulant activity as measured in the MLR assay, would be useful in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable, including viral infections such as HIV and Epstein-Barr, and cancers such as melanoma based on references cited in the art, including the Examiner cited references like Picotti *et al.* and Campo *et al.*

The Examiner also makes detailed arguments regarding the instant MLR controls and MLR's use in only determining histocompatibility. On Page 6, second paragraph, the Examiner says, "MLR is typically used for determining histocompatibility in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders,"

Appellants note that the MLR assay also depends upon the interactions of T lymphocytes with other cells, in particular, with the stimulator cells used in the described MLR protocol, as explained in the Fong declaration, and as shown in MLR assays performed within the Examiner cited references like Picotti *et al.* and Nishioka *et al.* T cells cooperate with antigen presenting cells like dendritic cells *in vivo,* which are the most potent antigen presenting cells, and are the predominant cell type found in the irradiated stimulator cell population as explained in the Fong Declaration (see paragraphs 5-6). Thus the MLR assay can and does measure the interaction of T-lymphocytes with other cells as well, and does not only measure histocompatibility of individuals.

Further, Appellants add that the Examiner appears to have misinterpreted the intent of the MLR assay in the instant application. The mixing of the stimulator and responder cells in the instant MLR is expected to lead to T cell proliferation even in the absence of any test protein. However, the point of the assay is to measure the extent to which the test protein can enhance the expected proliferation of the stimulated T cells.

The Examiner's misunderstanding of the instant MLR assay is further demonstrated in the Examiner's discussion of "controls" (page 6-7, last paragraph onwards of the Final Office Action mailed November 15, 2004). The Examiner has asserted that "(t)here are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. There is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls."

Appellants submit that these controls are only needed when the purpose of carrying out the MLR assay is to evaluate the properties of the stimulator cells. The purpose of the assay disclosed in the instant specification, as discussed above, is to characterize, not the stimulator cells, but the test proteins, such as PRO1375. The precise extent to which the stimulator cells stimulate the responder cells is not significant; what matters is the degree to which the test

protein increases this response. The extent to which the test protein increases the response of the T cells is measured by comparison to a negative control reaction, which uses either cell culture medium, or a non immunostimulant molecule, CD4-IgG, as a negative control. Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required.

In summary, Appellants respectfully submit that the Examiner has not shown that a lack of correlation typically exists between results of the MLR assay *in vitro* and immunomodulatory activity *in vivo*. In fact, references Picotti *et al.* and Campo *et al.* support the Appellants' position that it is more likely than not that the *in vitro* MLR assay can be successfully used to identify compounds having immunomodulatory activity *in vivo*. Therefore, the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible.

D. The Fong Declaration supports "real world" utility for proteins that test positive in the MLR assay

The Examiner asserted that "Dr. Fong's Declaration is fully considered, but is not effective to overcome the rejection....under 35 U.S.C. 101/112, first paragraph".

Appellants strongly disagree. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[18] "After evidence or argument is submitted by the Appellant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be

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[18] *In re Rinehart,* 531 F.2d 1084, 189 U.S.P.Q. 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 U.S.P.Q. 881 (Fed. Cir. 1985).

[19] *In re Alton,* 37 U.S.P.Q.2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)).

considered by an examiner"[20]. Appellants also respectfully draw the Board's attention to the Utility Examination Guidelines[21] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Thus, barring evidence to the contrary, Appellants maintain that the positive result for PRO1375 in the MLR assay is significant, and forms the basis for the utility claimed herein.

Further, the Examiner adds that "the MLR assay in itself is not predictive of an *in vivo* immune response, as was shown by Picotti *et al.*" While the Examiner acknowledges on page 11, line 1 of the Final Office action that "IL-12 is a known immune stimulator, which was first identified in an MLR assay," the Examiner later adds on page 11, line 19 that, "there are discrepancies of the effect of IL-2 on MLR assay depending on what stimulator is used." The Examiner cites Nishioka *et al.* as stating "IL-12 effects differentially in human or mice cellular immunity in MLR stimulated by dendritic cells. Although IL-12 is shown to suppress MLR in mice, IL-12 stimulates MLR in humans." Thus, the Examiner concludes that "the effect of IL-12 in the MLR assay alone was not sufficient to elucidate the role of this cytokine in the immune system." (Page 12 of the Final Office Action mailed November 15, 2004).

As discussed above, Picotti *et al.* in fact provides supportive evidence and confirms that that a given molecule (like IL-12) that may not accelerate allograft rejection *in vivo* may still possess properties of a general immunostimulant in cell mediated immune responses *in vivo* (see page 1459, col.1). Therefore, Picotti *et al.* is not an appropriate reference for rejecting the Fong declaration.

Morever, regarding the rejection of the Fong declaration based on Nishioka *et al.*, Appellants submit that the Nishioka *et al.* also provides supportive evidence for the Appellants' position that the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is in fact a widely used *in vitro* assay for identifying immunomodulatory compounds. For instance, Nishioka *et al.* themselves provide compelling reasons for the observed discrepancies that the

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[20] *In re Alton, supra.*

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

Examiner refers to in the rejection. The authors say on page 627, first column, second paragraph, line 10 that:

> "(t)hese discrepancies between the previous reports and ours might be a result of the differences of stimulator used in MLR. BM-DCs (bone marrow derived dendritic cells) were used in our experiments and splenocytes in the other as a stimulator. Splenocytes contain a DC population, but the percentage of DCs in the spleen is 1.0-1.6%. DCs are stronger stimulators in MLR when compared with splenocytes. Therefore, the stimulation by DCs might lead to a higher production of NO and the subsequent suppression of MLR."

The authors further acknowledged on page 626, in the second paragraph of the discussion section, that:

> "**IL-12 is known to play an important role in promoting Th1 differentiation and cellular immune responses**. The numerous studies demonstrated the antitumor effects of IL-12, whereas the detailed mechanisms remained unclear as a result of the complex effects of IL-12" (emphasis added).

The authors add on the last line of the discussion on page 627 that:

> "(a)s NO induced by IL-12 in vivo is likely to be less in humans, **the antitumor effect mediated by IL-12 via cellular immune responses might be expected in humans rather than in mice**" (emphasis added).

The authors conclude on the last line of the abstract that:

> "(t)hese results suggest that NO produced by DCs (dendritic cells) might play an important role in IL-12 mediated immune suppression in mice but not in humans."

Therefore, Appellants submit that the Examiner has not made a compelling case for rejecting the Fong Declaration based on the teachings of Picotti *et al.* or Nishioka *et al.*, because these references, in fact, support the Appellants' position that results from an MLR assay indicate an immunomodulatory activity for that molecule *in vivo*. Even if discrepancies between MLR studies by various groups may occur, a careful analysis of the materials used in the assay, for instance, the type of immune cells used like DCs (dendritic cells) versus splenocytes, mouse cells versus human cells, etc., can elucidate the reasons underlying the mechanism for the discrepancy as explained in Nishioka *et al.* Although such experiments further the understanding of the immunomodulatory mechanism, they are confirmatory studies, and would not be considered

undue by the skilled artisan. Moreover, they are not essential for utility determination of the molecule. Therefore, Appellants submit that this rejection is improper under both the case law and the Utility guidelines.

E. One Skilled in the Art would know how to make and use the variant proteins without undue experimentation based on the teachings in the art and in the specification

The Examiner had rejected the instant claims under 35 U.S.C. 112, first paragraph because "although the claims recite both percent identity and functional language, the specification does not disclose a variant of the polypeptide of SEQ ID NO:418 that induces proliferation of stimulated T lymphocytes in a MLR. Due to the large quantity of experimentation necessary to determine all the nucleic acids comprising a nuleotide sequence that is at least 80%, 85%, 90%, 95% or 99% identical to the polypeptide of SEQ ID NO:418 and to screen for the ones that induce proliferation of stimulated T lymphocytes in a MLR, the lack of direction/ guidance..., the complex nature of the invention, the absence of working examples..., the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the unpredictability of the effects of mutation on the structure and function of the claimed polypeptide, the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required...." (Page 8, line 8 onwards of the Final Office Action mailed November 15, 2004).

Appellants respectfully disagree. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[22] As discussed above, a considerable amount of experimentation is permissible, if it is merely routine.

Appellants refer to the arguments presented above with respect to utility and these arguments are incorporated by reference herein. Appellants note that the claimed nucleic acid variants all share the functional recitation that "wherein the polypeptide encoded by said nucleic acid induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction." Example 151 of the present application provides detailed protocols for the MLR assay, including

[22] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

the extensive step-by-step guidance from Current Protocols in Immunology, which is explicitly incorporated into the specification by reference. By following the disclosure in the specification, one skilled in the art can easily test whether a PRO1375 polypeptide, encoded by any variant nucleic acid claimed herein, is capable of stimulating proliferation of T-lymphocytes. Appellants recognize that there may be polypeptides, encoded by such variant nucleic acids, that are (i) structurally related to PRO1375 but which do not test positive in the MLR assay or, (ii) do not resemble PRO1375 in structure but stimulate the immune system through mechanisms unrelated to those of PRO1375. Such variant nucleic acids encoding the PRO1375 polypeptides described above however, would not be encompassed by the instant claims because Appellants claim only those variant nucleic acids that meet the structural requirements defined in the claims and whose encoding proteins meet the functional requirements defined in the claims. Thus, these recitations clearly act to further define the claimed genus of variant nucleic acids and this would be clearly evident to one of skill in the art.

The specification further describes methods for the determination of percent identity between two nucleic acid sequences. (See page 309-311, line 22). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Once such a nucleic acid sequence is identified, the specification sets forth methods for making the nucleic acid sequence (see page 309 and Example 135, page 511 of the specification), methods of preparing the corresponding PRO polypeptides (see page 375, line 11 and onward) and detailed guidance as to the changes that may be made to a PRO polypeptide without adversely affecting its activity (page 371, line 6, to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Accordingly, one of skill in the art could identify whether a variant nucleic acid sequence coding for a polypeptide of PRO1375 sequence falls within the parameters of the claimed invention.

Moreover, Appellants note that biological activity in this instance is not claimed based on structural similarity. Neither is structure prediction of the claimed variants a requirement for utility of the claimed polypeptides. As discussed above, Appellants claim only those nucleic acids which meet both recitations of the claims, structural and functional. Therefore the effects of mutations on structure-prediction of the variants and the unpredictability in the art are irrelevant to the instant

case. Finally, the breadth of the claims are clearly defined by both the structural and functional recitations.

Therefore, Appellants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a variant nucleic acid to determine whether it's encoding polypeptide is capable of stimulating proliferation of T-lymphocytes by the methods set forth in Example 151. One of skill in the art would have understood at the time of filing, based on the design of the instant MLR assay (which is designed to find molecules that increase DC (dendritic cell)-induced T-cell proliferation) and based solely upon the knowledge about DCs and their role in antigen presentation which was widely known that: (i) molecules which enhanced the proliferation of stimulated T-cells would increase the ability of DCs to convert antigens to immunogens, and (ii) such stimulatory molecules would allow antigens that were not usually immunogenic, such as the melanoma or viral antigens described above, to become immunogenic without undue experimentation. Thus, this biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed nucleic acid sequences without undue experimentation.

Accordingly, Appellants respectfully request reconsideration and reversal of the enablement rejection of Claims 119-127, 129-132 and 134-138 under 35 U.S.C. §112, first paragraph.

ISSUE III: Claims 119-127, 129-132 and 134-138 are not anticipated under 35 U.S.C. §102(b) by WO00/18904, WO99/63088, WO00/00610, WO00/00506 and further, are not anticipated under 102(a) by EP1130094

(i) Claims 119-127, 129-132 and 134-138 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by (b) over WO00/18904, (published June/2000); WO99/63088, (published September/1999); WO00/00610, (published June/2000); WO00/00506, (published June/2000).

Appellants submit that, as discussed above regarding the utility and enablement requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, (Issue II), the results of the MLR assay (Example 151) establishes a credible, substantial and specific asserted utility for the

claimed PRO1375 polypeptides. These results were first disclosed in U.S. Provisional Application Serial No. 60/144,758, filed on July 20, 1999 (discussed in Issue I). The disclosure of the instant application, which is similar to that of the earlier-filed application (U.S. Provisional Application Serial No. 60/144,758), provides the support required under 35 U.S.C. §112 for the subject matter of the instant claims. These arguments are incorporated by reference herein. Accordingly, Appellants submit that the subject matter of the instant claims is disclosed in the manner provided by 35 U.S.C. §112 in U.S. Provisional Application Serial No. 60/144,758. Therefore, the effective filing date of this application is July 20, 1999, the filing date of U.S. Provisional Application Serial No. 60/144,758.

That is, the instant application claims priority to U.S. Provisional Application Serial No. 60/144,758, filed on July 20, 1999, over six months before the publication date of WO00/18904, WO00/00610, WO00/00506, and at least one month before the publication date of WO99/63088, and first disclosed that the PRO1375 polypeptide tested positive in the MLR assay.

Accordingly, Appellants respectfully request reconsideration and reversal of the rejection of Claims 119-127, 129-132 and 134-138 under 35 U.S.C. §102(b) as being anticipated by WO00/18904, WO99/63088, WO00/00610, WO00/00506.

(ii) Claims 119-125, 127 and 129-138 stand rejected under 35 U.S.C. §102(a) as being anticipated by EP1130094, (published September/2001).

As discussed above, under Issue I: priority and Issue II: utility/enablement (the above arguments being incorporated by reference herein), the instant application correctly claims priority to U.S. Provisional Application Serial No. 60/144,758, and therefore, is at least entitled to an effective filing date of **July 20, 1999**. Accordingly, EP1130094 (published September/2001) is not prior art. Therefore, Appellants respectfully request reconsideration and reversal of the rejection of Claims 119-125, 127 and 129-138 under 35 U.S.C. §102(a).

CONCLUSION

For the reasons given above, Appellants submit that the MLR assay disclosed in Example 151 of the specification provides at least one patentable utility for the PRO1375 polypeptides, and for nucleic acids encoding the same as claimed in Claims 119-127, 129-132 and 134-138. Appellants further submit that one of ordinary skill in the art would understand how to use the claimed polypeptides, for example in therapeutic applications where enhancement of an immune response is beneficial, such as in the treatment of viral infections or cancer. Therefore, the corresponding encoding nucleic acids are also useful and Claims 119-127, 129-132 and 134-138 meet the requirements of 35 USC §101 and 35 USC §112, first paragraph. Further, this patentable utility for the instantly claimed nucleic acids was first disclosed in U.S. Provisional Application Serial No. 60/144,758, filed on July 20, 1999, priority to which is properly claimed in the instant application. Accordingly, the instant application has an effective priority date of July 20, 1999, and therefore neither WO00/18904, (published June/2000); WO99/63088, (published September/1999); WO00/00610, (published June/2000); WO00/00506, (published June/2000) nor EP1130094, (published September/2001) are prior art and do not anticipate the claims under 35 USC §102(a) or (b).

Accordingly, reversal of all the rejections of Claims 119-127, 129-132 and 134-138 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C71**).

Respectfully submitted,

Date: May 30, 2006

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8. CLAIMS APPENDIX

Claims on Appeal

119. An isolated nucleic acid having at least 80% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115;

wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction.

120. An isolated nucleic acid of Claim 119 having at least 85% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115;

wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction.

121. An isolated nucleic acid of Claim 119 having at least 90% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115;

wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction.

122. An isolated nucleic acid of Claim 119 having at least 95% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115;

wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction.

123. An isolated nucleic acid of Claim 119 having at least 99% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115;

wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction.

124. An isolated nucleic acid comprising:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115.

125. The isolated nucleic acid of Claim 124 comprising a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418.

126. The isolated nucleic acid of Claim 124 comprising a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide.

127. The isolated nucleic acid of Claim 124 comprising the nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide.

129. The isolated nucleic acid of Claim 124 comprising the nucleic acid sequence of SEQ ID NO: 417.

130. The isolated nucleic acid of Claim 124 comprising the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417.

131. The isolated nucleic acid of Claim 124 comprising the full-length coding sequence of the cDNA deposited under ATCC accession number 203115.

132. An isolated nucleic acid that hybridizes under stringent conditions to:

(a) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418;

(b) a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 418, lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 418;

(d) the nucleic acid sequence of SEQ ID NO: 417;

(e) the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 417; or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 203115;

wherein said stringent conditions employ hybridization using 50% formamide, 5X SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5X Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, and washes at 42°C in 0.2X SSC, at 55°C in 50% formamide followed by a high-stringency wash at 55°C in 0.1X SSC, EDTA.

134. The isolated nucleic acid of Claim 52 which is at least 10 nucleotides in length.

135. A vector comprising the nucleic acid of Claim 124.

136. The vector of Claim 135, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.

137. A host cell comprising the vector of Claim 135.

138. The host cell of Claim 137, wherein said cell is a CHO cell, an *E. coli* or a yeast cell.

9. EVIDENCE APPENDIX

1. Kahan, Barry D., "Immunosuppressive therapy," *Curr. Opin. Immunol.* **4**:553-560 (1992).

2. Picotti, J.R. et al., "Interleukin-12 (IL-12)-driven alloimmune responses in vitro and in vivo," *Transplantation* **67**:1453-1460 (1999).

3. Campo, C.A. et al., "Zinc inhibits the mixed lymphocyte culture," *Biological Trace Element Research*, **79**:15-22 (2001).

4. Nishioka, et al., "Differential effects of IL-12 on the generation of alloreactive CTL mediated by murine and human dendritic cells: a critical role for nitric oxide," *J. Leukocyte Biol.*, **73:** 621-629, (2003).

5. Declaration of Sherman Fong, Ph.D. under 35 C.F.R 1.132, with attached Exhibits A-E:

A. Current Protocols in Immunology, Vol. 1, Richard Coico, Series Ed., John Wiley & Sons, Inc., 1991, Unit 3.12.

B. Steinman, R.M., "The dendritic cell advantage: New focus for immune-based therapies," *Drug News Perspect.* **13**:581-586 (2000).

C. Gubler, U. et al., "Coexpression of two distinct genes is required to generate secreted bioactive cytotoxic lymphocyte maturation factor," *Proc. Natl. Acad. Sci. USA* **88**:4143-4147 (1991).

D. Peterson, A.C. et al., "Immunization with melan-A peptide-pulsed peripheral blood mononuclear cells plus recombinant human interleukin-12 induces clinical activity and T-cell responses in advanced melanoma," *J. Clin. Oncol.* **21**:2342-2348 (2003).

E. Thurner, B. et al., "Vaccination with Mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T cells and induces regression of some metastases in advanced stage IV melanoma," *J. Exp. Med.* **190**:1669-1678 (1999).

Items 1-4 were made of record by the Examiner in the Final Office Action mailed November 15, 2004.

Item 5 was submitted with Appellants' Response filed August 5, 2004, and noted as considered by the Examiner in the Final Office Action mailed November 15, 2004.

10. RELATED PROCEEDINGS APPENDIX

None - no decision rendered by a Court or the Board in any related proceedings identified above.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Docket No.:

Serial No.: Group Art Unit:

Filing Date: Examiner:

For:

DECLARATION OF SHERMAN FONG, Ph.D. UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Sherman Fong, Ph.D. declare and say as follows: -

1. I was awarded a Ph.D. in Microbiology by the University of California at Davis, CA in 1975.

2. After postdoctoral training and holding various research positions at Scripps Clinic and Research Foundation, La Jolla, CA, I joined Genentech, Inc., South San Francisco, CA in 1987. I am currently a Senior Scientist at the Department of Immunology/Discovery Research of Genentech, Inc.

3. My scientific Curriculum Vitae is attached to and forms part of this Declaration.

4. I am familiar with the Mixed Lymphocyte Reaction (MLR) assay, which has been used by me and others under my supervision, to test the immune stimulatory or immune inhibitory activity of novel polypeptides discovered in Genentech's Secreted Protein Discovery Initiative project.

5. The MLR assay is a well known and widely used proliferative assay of T-cell function, the basic protocols of which are described, for example, in Current Protocols in Immunology Vol. 1, Richard Coico, Series Ed., JohnWiley & Sons, Inc., 1991, Unit 3.12. (Exhibit A). This publication is incorporated by reference in the description of the MLR protocol in the present application.

6. The T-lymphocytes or "T-cells" of our immune system can be induced to proliferate by a variety of agents. The MLR assay is designed to study a particularly important induction mechanism whereby responsive T-cells are cultured together (or "mixed"), with other lymphocytes that are "allogeneic", e.g. lymphocytes that are taken from different individuals of the same species. In the MLR protocol of the present application, a suspension of PBMCs that includes responder T-cells, is cultured with allogeneic PBMCs that predominantly contain dendritic cells. According to the protocol, the allogeneic "stimulator" PBMCs are irradiated at a dose of 3000 Rad. This irradiation is done in order to create a sample of cells that has mainly dendritic cells. It is known that the dendritic cell population among the PBMCs are differentially affected by irradiation. At low doses (500-1000 Rad), the proliferation of most cells, including the B cells in the PBMCs, is preserved, however, at doses above 2000 Rad, this function of B cells is abolished. Dendritic cells on the other hand, maintain their antigen presentation function even at a 3000 Rad dose of radiation. (See, e.g. Current Protocols in Immunology, *supra*, at 3.12.9). Accordingly, under the conditions of the MLR assay used to test the PRO polypeptides of the present invention, the stimulator PBMCs remaining after irradiation are essentially dendritic cells.

7. Dendritic cells are the most potent antigen-presenting cells, which are able to "prime" naive T cells *in vivo*. They carry on their surface high levels of major histocompatibility complex (MHC) products, the primary antigens for stimulating T-cell proliferation. Dendritic cells provide the T-cells with potent and needed accessory or costimulatory substances, in addition to giving them the T-cell maturing antigenic signal to begin proliferation and carry out their function. Once activated by dendritic cells, the T-cells are capable of interacting with other antigen presenting B cells and macrophages to produce additional immune responses from these cells. For further details about the properties and role of dendritic cells in immune-based therapies see, e.g. Steinman, Drug News Perspect. 13(10):581-586 (Exhibit B).

8. The MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously.

9. Such immune stimulants find important clinical applications. For example, IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. IL-12 was first identified in just such an MLR [Gubler et al. PNAS 88, 4143 (1991) (Exhibit C)]. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson et al. Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)] They extracted circulating white blood cells carrying one or more markers of melanoma cells, isolated the antigen, and returned them to the patients. Normally patients would not have an immune response to his or her own human antigens. The patients were then treated with different doses of IL-12, an immune stimulant capable of inducing the proliferation of T cells that have been co-stimulated by dendritic cells. Due to the immune stimulatory effect of IL-12, the treatment provided superior results in comparison to earlier work, where patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs), treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response. [Thurner et al. J. Exp. Med. 190 (11), 1669-78 (1999) (Exhibit E)].

10. It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant. Some PRO polypeptides do the reverse, and give inhibition of T-cell proliferation in the MLR assay. It is my considered scientific opinion that a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases.

Dated: 6/16/04

By: Sherman Fong

Sherman Fong, Ph.D.

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